

The Impact of Acupuncture on Improvement of Female
Fertility through Reduction of Stress and Anxiety

A Capstone Project

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Doctor of Acupuncture and Oriental Medicine

By

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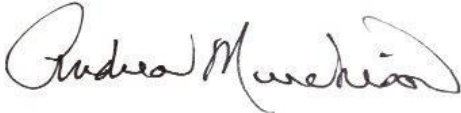
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Abstract

Fertility rates have been declining in the USA by 7.3% between the years of 2007 and 2011, with continuously larger number of women unable to conceive. Fertility is also declining to below the replacement rate globally, in many industrialized countries such as Germany, Finland and Japan, and various assisted reproductive technologies are increasingly being used to facilitate pregnancy and live births. Given the current situation of decreased fertility, the goal of this research synthesis was to examine the existing body of research and to get a better understanding about how stress and anxiety might negatively impact fertility and how acupuncture could potentially contribute to the improvement of fertility by reducing stress and anxiety. On the basis of the results of the current study implications for theory and practice and recommendations regarding the direction of future research were discussed.

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Chapter 1 – Introduction

Overview

Fertility and births have been declining in the USA, with continuously larger number of women unable to conceive. The National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDCP) report that the provisional fertility rate declined by 7.3%, between 2007 and 2011, from 69.5 births per 1,000 of women age 15 – 44, to 64.4 births per 1,000 women age 15 – 44; and that the provisional count of births declined by 7.8% between 2007 and 2011, from 4,316,233 to 3,978,000 (Hamilton & Sutton, 2012). Fertility is also declining to below the replacement rate globally, in many industrialized countries such as Germany, Finland and Japan, and various assisted reproductive technologies are increasingly being used to facilitate pregnancy and live births (Nakamura, K., Sheps, S., & Arck, P. C., 2008). Given these current downward trends in fertility, it is helpful to find out what are some of the causes underlying the decline in fertility, and specifically the impact of psychological factors such as stress and anxiety on fertility, and how modalities, like acupuncture, may positively impact fertility and fecundity under conditions of stress and anxiety.

Research Question and Hypothesis

It is generally established that stress and anxiety can lead to infertility, the lack of ability to reproduce. This study hypothesized that acupuncture has the ability to lower stress and anxiety and therefore alleviate their negative impact on fertility. The research questions posed regarding the current study are as follows:

- How can acupuncture reduce stress and anxiety and, in turn, improve fertility?
- What is the impact of stress and anxiety on fertility?

- What role can acupuncture play in reducing stress and anxiety?

Definition of Key Terms

Adenohypophysis is the anterior part of the pituitary gland that is derived from the embryonic pharynx and is primarily glandular in nature—called also *anterior lobe* (Pease, R. W., & Merriam-Webster, Inc., 2006).

Adrenalin is a hormone produced by the adrenal medulla. Its function is to aid in the regulation of the sympathetic branch of the autonomic nervous system. At times when a person is highly stimulated, as by fear, anger, or some challenging situation, extra amounts of epinephrine are released into the bloodstream, preparing the body for energetic action (Farlex Partner Medical Dictionary © Farlex 2012).

Adrenocorticotrophic Hormone (ACTH) is a hormone of the adenohypophysis that stimulates growth of the adrenal cortex and the synthesis and secretion of corticosteroids. ACTH secretion, regulated by corticotrophin-releasing hormone (CRH) from the hypothalamus, increases in response to a low level of circulating cortisol and to stress, fever, acute hypoglycemia, and major surgery (Farlex Partner Medical Dictionary © Farlex 2012) .

Androgen is a steroid hormone which promotes male characteristics. The two main androgens are androstenedione and testosterone (Farlex Partner Medical Dictionary © Farlex 2012).

Anxiety is a feeling of fear, unease, and worry (United States & National Institute of Health (US), 2003).

Assisted Reproductive Technology (ART) includes all fertility treatments in which both eggs and sperm are handled. In general, ART procedures involve surgically removing eggs from a woman's ovaries, combining them with sperm in the laboratory, and returning them to the

The Impact of Acupuncture on Improvement of Female Fertility through Reduction of Stress and Anxiety woman's body or donating them to another woman. They do not include treatments in which only sperm are handled (i.e., intrauterine—or artificial—insemination) or procedures in which a woman takes medicine only to stimulate egg production without the intention of having eggs retrieved (Center for Disease Control and Prevention, 1992).

Beta Endorphins are naturally occurring opiate neurotransmitter released when the body is under stress (Farlex Partner Medical Dictionary © Farlex 2012).

Cortisol is an adrenal hormone produced in response to stress (Farlex Partner Medical Dictionary © Farlex 2012).

Corticosteroids are group of natural hormones secreted by the hypothalamic-anterior pituitary-adrenocortical (HPA) axis, more commonly referred to as the pituitary gland. These include glucocorticoids, which are anti-inflammatory agents with a large number of other functions; mineralocorticoids, which control salt and water balance primarily through action on the kidneys; and corticotrophins, which control secretion of hormones by the pituitary gland (Farlex Partner Medical Dictionary © Farlex 2012).

Corticotrophin Releasing Hormone (CRH) a polypeptide hormone secreted by the hypothalamus into the pituitary portal system where it triggers the release of adrenocorticotrophic hormone (ACTH) from the pituitary gland (Farlex Partner Medical Dictionary © Farlex 2012).

Downregulation is the development of a tolerant state consequent on repeated administration of a pharmacologically or physiologically active substance; often accompanied by an initial decrease in affinity of receptors for the agent and a subsequent diminution in the number of

The Impact of Acupuncture on Improvement of Female Fertility through Reduction of Stress and Anxiety receptors. It is the reduction of a cell's response to a hormone (Farlex Partner Medical Dictionary © Farlex 2012).

Estrogens are the female sex hormones, including estradiol, estriol, and estrone. In humans, the estrogens are formed in the ovary, adrenal cortex, testis, and fetoplacental unit, and are responsible for female secondary sex characteristic development, and, during the menstrual cycle, act on the female genitalia to produce an environment suitable for fertilization, implantation, and nutrition of the early embryo (Farlex Partner Medical Dictionary © Farlex 2012).

Fertility is the body's natural capability to produce off-springs, the capacity to conceive or to induce conception (Farlex Partner Medical Dictionary © Farlex 2012).

Fecundity is the biological capacity to reproduce, irrespective of pregnancy intentions (Lynch et al., 2012).

Follicle-Stimulating Hormone (FSH) is a glycoprotein hormone of the anterior pituitary gland that stimulates the Graafian follicles and assists in follicular maturation and in the secretion of estradiol. It also stimulates the epithelium of the seminiferous tubules and assists in inducing spermatogenesis (Farlex Partner Medical Dictionary © Farlex 2012).

Glucocorticoids are a group of corticosteroid hormones (mainly *cortisol*, of which *cortisone* is the precursor) produced by the adrenal cortex, under the control of adrenocorticotrophic hormone (ACTH) from the anterior pituitary. Their major actions on nutrient metabolism have the net effect of promoting glucose and free fatty acid availability as fuels. They are also vital for normal cellular processes as diverse, for example, as excitation-contraction coupling and the health of connective tissues (Farlex Partner Medical Dictionary © Farlex 2012).

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Glucocorticoid Receptor is a protein found in multiple forms within cells, which binds glucocorticoids and subsequently influences gene transcription (Retrieved from <http://www.yourdictionary.com/glucocorticoid-receptor>).

Gonadotropin-releasing hormone (GnRH) is a hormone produced by the hypothalamus that stimulates the anterior pituitary gland to begin secreting luteinizing hormone and follicle-stimulating hormone (Farlex Partner Medical Dictionary © Farlex 2012).

Hormone is a chemical substance produced in the body which has a specific regulatory effect on the activity of certain cells or a certain organ or organs (Farlex Partner Medical Dictionary © Farlex 2012).

Infertility is the inability to conceive after one year of sexual relations without contraception, or the inability to carry pregnancy to a live birth (Farlex Partner Medical Dictionary © Farlex 2012).

In Vitro Fertilization (IVF) is the process of fertilization by manually combining an egg and sperm in a laboratory dish. When the IVF procedure is successful, the process is combined with a procedure known as embryo transfer, which involves physically placing the embryo in the uterus (Retrieved from <http://www.webmd.com/infertility-and-reproduction/guide/in-vitro-fertilization>).

Luteinizing Hormone is a hormone produced by the anterior lobe of the pituitary gland that stimulates ovulation and the development of the corpus luteum in the female and the production of testosterone by the interstitial cells of the testis in the male (Farlex Partner Medical Dictionary © Farlex 2012).

Pregnanediol is a chief steroid metabolite of progesterone that is biologically inactive and occurs as pregnanediol glucuronate in the urine (Farlex Partner Medical Dictionary © Farlex 2012).

Progesterone is a steroid hormone secreted by the corpus luteum, the adrenal cortex, and by the placenta, that acts to prepare the uterus for implantation of the fertilized ovum, to maintain pregnancy, and to promote development of the mammary glands (Farlex Partner Medical Dictionary © Farlex 2012).

Stress is a state of mental or emotional strain or tension resulting from adverse or very demanding circumstances. Physiologically, stress represents “the response of an organism to challenges to its dynamic equilibrium or homeostasis” (Nepomnaschy et al., 2007, P.352).

Upregulation is opposite of downregulation (Farlex Partner Medical Dictionary © Farlex 2012).

Chapter 2: Review of Literature

Introduction

This study researched the impact of acupuncture on improvement of female fertility through reduction of stress and anxiety. It looked at how stress and anxiety can negatively impact fertility in women, how acupuncture can reduce stress and anxiety, and how acupuncture can improve female fertility through the reduction of stress and anxiety.

Online search of medical journals, and other published, peer reviewed articles were performed through PUBMED, EPSCOHOST, NIH, Fertility and Sterility, and Google Scholar. Search words used were stress and female fertility, anxiety, acupuncture and stress reduction, acupuncture and infertility, female hormones and stress, cortisol, adrenalin, sympathetic nervous system. Articles selected included research done in the USA, England, Australia and China. All articles included were in English or in English translation. Of the 459 articles that were identified to have some relevance to the topic of this paper, 33 articles were selected meeting the eligibility criteria for inclusion in the current study. Published books and class notes were also used.

To understand how acupuncture can improve female fertility by reducing stress and anxiety we must first understand how stress and anxiety can impact fertility. Then, we need to understand how acupuncture can reduce stress and anxiety. By understanding these two variables, impact of stress and anxiety on fertility and acupuncture's ability to relieve stress and anxiety, we will be able to correlate how acupuncture could improve female fertility under these conditions.

This literature review chapter begins with the presentation of brief definitions of stress and anxiety, and bio-markers of stress. That section is followed by a brief consideration of the research that links stress and anxiety with infertility. The consideration of current literature regarding the impact of acupuncture on stress and anxiety follows. Then, a review of the research regarding the ability of acupuncture to improve fertility by reducing stress and anxiety will be presented. The chapter concludes with a brief literature review integration section.

Definitions of Stress and Anxiety, and Bio-Markers of Stress

The concept of stress, even though not named as such then, dates back to 400 B.C. with Hippocrates, who recognized diseases as states of disequilibrium and imbalance and defined natural causes of diseases as stressors (Chrousos, G. P., Loriaux, D. L., & Gold, P. W., 1988). Hippocrates also recognized that disease is not only “pathos” (suffering), but also “pronos” (toil) arising as the body fights back to restore balance and normalcy. In Physics, stress is an internal opposing force to an external force and is measured per unit of area. Stress is also a concept which is used to explain elasticity which is the property by which an object retains its original shape and size. The first use of the word stress was by Hans Selye (1907-1982) who, as a student, observed that patients suffering from different diseases often exhibited identical signs and symptoms that made them look sick. He later described this as a General Adaptation Syndrome, a response of the body to demands placed upon it. He also details how stress induced hormonal autonomic responses, over time, can lead to various diseases (Rosch, 1998).

There are several definitions of stress and anxiety depending on the sources consulted. However, there is a common thread that defines these concepts: stress is a challenge to homeostasis, a balanced state of the body (Nepomnaschy, 2004; Levine, 2005). Stress is also a

The Impact of Acupuncture on Improvement of Female Fertility through Reduction of Stress and Anxiety feeling of emotional or physical tension. Anxiety is a feeling of fear, unease, and worry (United States & National Institute of Health (US), 2003).

In moderate amounts stress can be useful in that it prepares the body for action and adaptation. The natural response of the body to stress is to produce stress hormones, especially cortisol and adrenalin, and to activate the sympathetic nervous system which enables the body to cope with stress. If the stress exceeds a certain threshold, which is dependent on individual ability to adapt to stress, it can be detrimental to many levels of health: physiological, behavioral, subjective experience, and cognitive (Levine, 2005).

This section of the paper looked at the physiological aspect of stress and anxiety as they impact fertility. The stress response activates the Hypothalamic-Pituitary-Adrenal (HPA) axis which releases certain neuro-endocrine hormones to neutralize the effects of stress. The Hypothalamus releases corticotrophin-releasing hormone (CRH) (Ferin, 1999). The pituitary gland, in response to the increase in CRH, releases the adrenocorticotropic (ACTH) hormone which acts upon the adrenals to release glucocorticoids (GCs) like cortisol and adrenalin (Levine, 2005).

While these stress hormones allow our bodies to successfully overcome stressful situations, their increase has also been associated with reduced ability to conceive. The following section explores the relationship between stress and anxiety and fertility.

Impact of Stress and Anxiety on Female Fertility

The role of stress and anxiety in the female reproductive process is not yet completely understood. In addition to the stressful impact of individual stressors or specific events, like loss of job, death of a family member, loss of the house, and other traumatic situations there is

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an inherent stress and anxiety in day-to-day life that also must be studied to expand our understanding of the interaction between stress, anxiety, and reproduction (Nepomnaschy et al., 2004).

Stress and anxiety of modern day-to-day life may potentially impede fertility through a complex mechanism. Some researchers such as J. Cwikel and associates (2004) hypothesized a multi-level relationship between psychological factors like stress and anxiety and fertility. They highlighted a three-fold relationship between psychological factors and infertility: psychological factors may lead to infertility; psychological stress may result from the diagnosis of infertility; and psychological factors and infertility may have a reciprocal relationship, impacting each other negatively. This section focuses mostly on the first relationship of how stress and anxiety could lead to infertility.

The complexity of the impact of stress and anxiety on female fertility has been researched in many studies. Some studies focus on the possible correlation between the HPA axis and the hypothalamic-pituitary-gonadal (HPG) axis and hypothesize that increased levels of CRH and cortisol may inhibit the activity of the HPG axis (Cwikel et al., 2004).

Nepomnaschy and associates (2004) believed that a trigger in CRH because of stress could negatively impact the pulsatility of the hypothalamic gonadotropin-releasing hormone (GnRH) and the surge in cortisol causes the pituitary gland to have a reduced response to the GnRH. GnRH stimulates the pituitary gland to produce luteinizing hormone (LH) and, to a lesser extent, follicle-stimulating hormone (FSH). Therefore, any disturbance in its release can lead to a delay or prevention of ovulation.

Koopman (2013) reported that an increase in cortisol levels due to stress results in a reduction of LH in the ovaries, disrupting ovulation. She also noted that a lower level of adrenalin in IVF patients increases the rates of implantation.

The increase in cortisol levels in response to stress has been shown to impact negatively the levels of certain reproductive hormones like gonadotropin, estrogen, progestin, and prolactin, leading to decreased fertility. This observation also supports the fact that there seems to be a correlation between the HPA and the HPG axes (Nepomnaschy et al., 2004; Nakamura et al. 2008; Magarelli et al., 2009).

The negative effect of stress and anxiety on women's fertility has been the subject of many other studies. Nepomnaschy and associates (2004) conducted a one year longitudinal study of stress and women's reproduction in a Mayan community in rural Guatemala by focusing on the cumulative effects of day-to-day life stress (Nepomnaschy et al., 2004). He studied a sample of 92 menstrual cycles provided by 24 women and evaluated the association between daily urinary cortisol levels and the reproductive hormones estrone conjugates (E1C), pregnandiol glucuronide (PdG), a urinary marker of progesterone, luteinizing hormone (LH), and follicle stimulating hormone (FSH). The conclusion of the study was that increases in the level of cortisol may have major negative impact on a woman's reproductive hormones over the entire menstrual cycle, as follows:

- During the follicular phase, there was an association between estrogen and increased levels of progesterone. Too much progesterone during the follicular phase is associated with a decrease in estrogen and can impact follicular development and the LH surge.

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- A reduction of estrogen as a result of increased cortisol jeopardized ovulation and the luteinization process.
- During the luteal phase, a lower level of progesterone was observed, negatively impacting the implantation process by preventing the proper development of the endometrium.

By using as subjects the women of a rural, traditional, small community, Nepomnaschy and associates (2004) assessed the impact of day to day stress on a socially, ethnically and economically homogeneous sample. The social structure revolved around family and migration was rare. This design allowed for less confounding factors to be controlled than in an urban setting and less complex stressors. This approach however, raises questions about its application to a heterogeneous, urban, industrialized population, where stressors are varied and possibly more intense than in an urban environment. The population's adaptability to stress would also be a factor to consider in assessing the impact of stress on fertility.

Nakamura and associates (2008) summarized some of the findings of various articles related to stress and reproductive failures and reached similar conclusions: excessive production of cortisol in response to stress can negatively impact follicular development, LH surge, luteal development and implantation. Baird and associates (1999) performed a longitudinal study to examine the hormonal predictors of conception in menstrual cycles of 215 healthy women. The authors used the data from the study to describe the hormonal patterns of natural conception cycles and to compare them with non-conception cycles. One of their conclusions was that the occurrence of a high level of baseline progesterone could be attributed to hyper-stimulation of the adrenals by stress and it might have anti-fertility effect by reducing the level of estrogen

The Impact of Acupuncture on Improvement of Female Fertility through Reduction of Stress and Anxiety and progesterone in the endometrial tissue, impacting proper maturation of the endometrium. This condition will prevent implantation and conception.

Lynch, C. D., Sundaram, R., Buck Louis, G. M., Lum, K. J., & Pyper, C., (2012) performed a prospective cohort study in the U.K. of 339 women trying to conceive and used a self-reporting psychological measurement tool as well as measurements of stress biomarkers of cortisol and alpha-amylase to assess the impact of stress on fecundability. They found no association between most psychological measures and fecundability odds ratio. They also found no correlation between the self-reported scores on the psychosocial questionnaires and the stress biomarkers. One reason might be that the women in the study did not report high levels of stress and anxiety. They found however that fecundability may increase when the women had a high level of social support.

Animal Studies

Based on animal studies, Ferin (1999) observed a potential inhibition of the HPG axis by noting a decrease of the hypothalamic GnRH pulse generator through the activation of the HPA axis by stress and anxiety. He proposed that this condition could be responsible for chronic anovulation, therefore inability to conceive.

Wagenmaker and associates (2009) performed experiments on ewes to analyze the impact of increased levels of cortisol infused during the pre LH surge on the LH surge. They noticed that cortisol delayed but did not block the LH surge, and concluded that elevation in plasma cortisol can interfere with the action of estradiol during the follicular phase by disrupting the neuroendocrine response to the positive action of estradiol by suppressing the GnRH pulsations and LH secretion, therefore delaying and attenuating the LH surge. Without

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the LH surge there can be no ovulation thus reproduction is impossible. By ovariectomizing the sheep and artificially inducing the estrous cycles through sequential administration of estrogen and progesterone and by artificially creating a stress response through the administration of plasma cortisol, the authors of these experiments were able to measure certain physiological responses related to stress and the reproduction cycle. However, it is uncertain how this process could correlate with the human population in its natural state.

Table 1 in Chapter 4 summarizes the findings of several articles related to the impact of stress and anxiety (S&A) on female fertility. It depicts the authors' names, the correlation of S&A to fertility, the phases of the menstrual cycle impacted by S&A, the HPA hormones and the HPG/HPO hormones analyzed in the various studies. This table shows a correlation between S&A and the hormones of the HPA and HPG/HPO axes and the various phases of the menstrual cycle. One could infer that a change in the HPA axis because of stress and anxiety could substantially impact the HPG/HPO axis to the point where proper hormonal balance needed for conception gets disrupted, therefore preventing conception.

Impact of Acupuncture on Stress and Anxiety

Acupuncture is a part of a medical system that has its roots in ancient China and has been practiced for thousands of years. It consists of insertion of very fine, filiform, stainless steel, sterile needles in various and specific points on the body for the purpose of soliciting a healing response. Acupuncture does not target a specific pathological function per se but achieves results by aiding the body in its capacity to restore its health and by promoting homeostasis (Ma, Y., Ma, M., & Cho, Z.-H., 2005).

Acupuncture has been extensively studied for its capacity to alleviate stress and anxiety. Pilkington, K., Kirkwood, G., Rampes, H., Cummings, M., & Richardson, J. (2007) performed a literature review of 919 studies related to anxiety and anxiety disorders and impact of acupuncture on the two conditions. They excluded 809 studies as being non relevant. Of the remaining studies they selected 12 randomized controlled trials (RCTs) for analysis; four randomized control studies focused on acupuncture in generalized anxiety disorder or anxiety neurosis and six of them focused on anxiety in the perioperative period. The evaluation tools were self-reporting of symptoms and lacked neutrality; no bio-markers were assessed in the RCTs. They concluded that, in general, they found positive results from acupuncture in all the 10 RCTs, but it was difficult to interpret the findings of the studies because of lack of details on methodology and homogeneity of the acupuncture intervention.

In 2010, Pilkington reported on some clinical studies that have assessed changes in levels of neurotransmitters and other biological response modifiers when assessing the specific biological actions of acupuncture on depression and anxiety. Changes in levels of corticosteroids, ACTH, and platelet serotonin were measured and the impact of acupuncture on these neuro-hormones was assessed. Statistically significant reductions in ACTH and platelet count of serotonin were found because of acupuncture but no significant change was found in the level of corticosteroids. She concluded that studies in this area of biomarkers and anxiety are few and results are preliminary.

In 2012, Errington-Evans selected 32 research articles from the body of research available and performed a literature review to investigate the use of acupuncture in the treatment of anxiety disorders. The conclusions were similar to Pilkington and associates

The Impact of Acupuncture on Improvement of Female Fertility through Reduction of Stress and Anxiety (2007) that the use of acupuncture for anxiety disorders results in statistically significant improvements but the methodology used to determine the results is lacking in areas such as frequency of sessions, acupuncture point selection and number, duration of treatment, rational for using the points, adequate dosage, repeatability and constancy of treatment, and correct technique.

Animal Studies

Perhaps the most relevant study to this paper showing the impact of acupuncture on stress and anxiety is the study performed by Wang, S. J., Zhang, J. J., & Qie, L. L. in 2014 on rats, showing the regulatory impact of acupuncture on stress reaction was achieved through the regulation of the HPA axis and that the point specificity matters in the achievement of the desired results. Wang and his associates (2014) performed experiments on 58 rats distributed in 5 groups. One control group was comprised of normal rats with no stress and no acupuncture intervention. A second group was not subjected to stress but received electro-acupuncture (EA) on points Lr-14 and BI-23. Another control group was subjected to stress but received no acupuncture. The other 2 groups were all impacted by stress and received electro-acupuncture; one group on points Sp-6 and Ki-9, the other group on Lr-14 and BI-23.

The authors of the experiment measured the impact of acupuncture on the regulation of the glucocorticoid receptors (GRs) which are extensively distributed in the central nervous system and which play a role in the negative feedback regulation of the GC on the HPA axis. After the adrenals secrete GC in response to stress, the GC adjusts the CRH secretion in the Hypothalamus and contributes to the inhibition of the stress reaction through the GRs. When the rats were exposed to stress there was a decrease of GRs expression in the hypothalamus

The Impact of Acupuncture on Improvement of Female Fertility through Reduction of Stress and Anxiety and in the pituitary gland and an increase in GRs expression in the adrenal cortex, commensurate with the chronic stress response. Acupuncture achieved a dual-directional regulation of the GRs expression: it down regulated the GR expression in the adrenal cortex and up regulated the GRs expression in the hypothalamus and the pituitary, helping to inhibit the stress response. Acupuncture was also shown to reduce the CRH expression in the hypothalamus and pituitary and to inhibit the ACTH receptors in the pituitary and adrenal cortex. The use of Lr-14 and Bl-23 was more effective than the use of Sp-6 and Ki-9, proving that point specificity matters. This is a promising example of how acupuncture could restore the body's innate ability to regulate stress by achieving homeostasis or normal balance of the HPA axis.

Impact of Acupuncture on Fertility by Reducing Stress and Anxiety

Several studies were done to assess the role of acupuncture in improving fertility. A common theme emerged when some researchers reviewed existing literature on the topic (Chang, R., Chung, P. H., & Rosenwaks, Z., 2002; Ng, E. H., So, W. S., Gao, J., Wong, Y. Y., & Ho, P. C., 2008). They inferred that because of its ability to increase beta-endorphins and endogenous opioids, acupuncture has an impact on reducing stress and anxiety. Acupuncture could also potentially regulate the Hypothalamus-Pituitary-Ovarian (HPO) axis; beta-endorphins have an impact on the GnRH secretion by the hypothalamus and on the menstrual cycle because the hypothalamic beta-endorphins' center and the GnRH pulse generator are both situated in the same region of the hypothalamus, the arcuate nucleus. Therefore, they also noted the impact that acupuncture has on ovulation and fertility and in the regulation of plasma levels of FSH, LH, E2, and progesterone (P). Some peripheral benefits of acupuncture in

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fertility were the reduction of artery impedance in the uterus which is beneficial to increasing the blood level in the uterus and to increasing endometrial thickness, improving the chances of implantation.

A series of experimental studies were performed on 10 chronically anovulatory women and on ovariectomized rats to assess the impact of electro-acupuncture on the regulation of the HPO axis (Chen, B. Y., 1997). The points used on the women were Rn-4, Rn-3, Sp-6, and Zigong, stimulated for 30 minutes with electro-acupuncture. The points used on the rats were Rn-4, Rn-3, Sp-6, and Zigong for 3 days followed by SJ-5 and Huatuojiayi points. Among the conclusions reached from the experiments were: electro-acupuncture has a regulatory action on the HPO axis and it may be through the impact on the HPA axis. The women who were subjected to electro-acupuncture and achieved ovulation showed a reduction in or a normal level of beta-endorphins while the beta-endorphins of the anovulatory women were of a substantially higher level. In addition, ovulatory women due to EA showed normalized levels of LH and FSH. From the experiments on the rats, Chen concluded that electro-acupuncture normalized the level of estrogen in the ovariectomized rats with lower than normal estrogen level. They also noticed an increase of the adrenal glands after EA and hypothesized that the changes in the level of estrogen could potentially be due to the action of EA on the HPA axis: the acupuncture may increase the synthesis and release of adrenal corticosteroids, including androgen. Androgen can be transformed into estrogen, restoring the negative feedback on the HPO axis. In addition, GnRH and LH could be normalized through the ability of EA to accelerate the release of brain and pituitary beta-endorphins. Like Wang and Associates (2014), Chen concluded point specificity matters and recommended 30 minutes of EA to achieve results.

In Australia, a randomized controlled trial of acupuncture was conducted at the University of Western Sydney to examine the effectiveness of acupuncture in reducing infertility-related stress (Smith, C. A., Ussher, J. M., Perz, J., Carmady, B., & de, L. S., 2011). The participants were 32 women, 20 to 45 years of age, unable to conceive within a period of 12 months. Acupuncture was administered in six treatments over 8 weeks and consisted of TCM and 5 Element style of acupuncture, focusing on the causative factor (CF) of the individual participants. Points used were upper chest kidney points and Pc-6, Pc-5, Ht-5, and Ht-7. The results showed benefits of acupuncture in reducing stress and creating some overall calmness based on individual, subjective measures, but there was no follow-up performed to find out if conception was facilitated after acupuncture. The sample size was too small to be significant and there were no bio-markers analyzed to support the subjective results.

Impact of Acupuncture on IVF

In researching studies done to explore the role of acupuncture in improving fertility by reducing stress, there were several articles reporting on how acupuncture reduced the pre- and post- embryo transfer (ET) stress levels resulting in improvement of IVF results. Balk, J., Catov, J., Horn, B., Gecki, K., & Wakim, A. (2010) performed an observational prospective cohort study to determine how acupuncture impacts perceived stress levels in 57 women on the day of embryo transfer (ET), and to determine if perceived stress levels at embryo transfer correlated with pregnancy rates. They observed that acupuncture reduced both pre- and post- ET stress levels and, women who showed this decreased level of stress, achieved higher pregnancy rate (64.7% in women who received acupuncture versus 42.5% in those who did not receive

The Impact of Acupuncture on Improvement of Female Fertility through Reduction of Stress and Anxiety (acupuncture treatments) and concluded that a reduced perceived stress level at the time of embryo transfer may improve pregnancy rates.

Other prospective randomized controlled clinical studies resulted in similar conclusions that women with lower stress levels during the luteal phase achieved higher pregnancy rates (Dieterle, S., Ying, G., Hatzmann, W., & Neuer, A., 2006; Turner, K., Reynolds-May, M. F., Zitek, E. M., Tisdale, R. L., Carlisle, A. B., & Westphal, L. M., 2013).

Acupuncture's positive role in improving the outcome of IVF has been documented in at least two other prospective randomized trials (Paulus, W. E., Zhang, M., Strehler, E., El-Danasouri, I., & Sterzik, K., 2002; Westergaard, L. G., Mao, Q., Kroglund, M., Sandrini, S., Lenz, S., & Grinsted, J., 2006). The researchers concluded that acupuncture can play a role in increasing the rate of pregnancy of IVF and also emphasized that acupuncture, by increasing the levels of beta-endorphins, could play a role in regulating the HPO axis.

Magarelli, P. C., Cridennda, D. K., & Cohen, M. (2009), observed increased rates of IVF outcomes and a regulation of cortisol (CORT) and prolactin (PRL) to effective levels in patients receiving acupuncture (Ac) treatments, resulting in reduced stress, during a prospective cohort clinical study on 67 women. This is another study that shows how acupuncture appears to have the ability to restore homeostasis and the body's natural ability to restore its health. The acupuncture treatments employed were of longer duration than just pre- and post- ET, for a total of 11 treatments.

Within the articles selected, there was one randomized, controlled, double blinded study with an independent observer that evaluated the influence of true versus sham acupuncture performed 25 minutes before and after ET on pregnancy rates in 160 women

The Impact of Acupuncture on Improvement of Female Fertility through Reduction of Stress and Anxiety undergoing IVF treatments and concluded that there was no significant difference on pregnancy rates between sham and true acupuncture; the sham acupuncture actually achieved higher pregnancy rates (Moy, I., Milad, M. P., Barnes, R., Confino, E., Kazer, R. R., & Zhang, X., 2011).

Literature Review Integration

Research showed that stress and anxiety have a negative impact on female fertility (Nepomnaschy et al., 2004; Cwikel et al., 2004; Ferin, 1999; Koopman, 2013; Nakamura et al., 2008; Magarelli et al., 2009). Increased levels of stress hormones negatively impact the balance of certain reproductive hormones, thus impeding fertility (Baird et al., 1999; Wagenmacher et al., 2009). Acupuncture has been shown to alleviate the physical and emotional symptoms of stress and anxiety (Pilkington et al., 2007; Errington-Evans, 2012; Wang et al., 2014). While acupuncture is believed to improve fertility, there is little research that details acupuncture's role in improving stress and anxiety and fertility. In addition, very little has been done to integrate acupuncture with western fertility medicine approaches. This research study addressed this gap by bringing together the most current research and theory regarding the role of stress and anxiety in fertility and how acupuncture can be used to decrease stress and anxiety to enhance fertility.

Chapter 3 – Methods

The objective of this study was to research the impact of Acupuncture on improvement of female fertility through reduction of stress and anxiety. This study examined how stress and anxiety can negatively impact fertility in women, how acupuncture can reduce stress and anxiety, and how acupuncture can improve female fertility through the reduction of stress and anxiety.

Research Synthesis

The methodology used was research synthesis, a systematic literature review, with primarily qualitative analysis, supported by some quantitative analysis, where appropriate. According to Cooper & Cooper (2010), research synthesis looks at past research and attempts to summarize overall conclusions from the various studies that address related or identical hypotheses. The goal of the researcher is to present the current state of knowledge related to the area of study and to highlight important issues that are still unresolved.

Sampling and Inclusion/Exclusion Criteria

Data for this study included the literature that was reviewed for Chapter Two of this study. The study included research syntheses and other studies from 1990 or later from the United States and other countries. Human and animal studies have also been included, as appropriate. Only peer-reviewed articles were used. Only articles that pertained to women between 20 and 45 years of age and of any ethnicity are included.

Excluded from the study were articles that pertained to women younger than 20 and older than 45 years of age, men of any age, and any articles or research data prior to 1990. Articles which described the role of therapeutic herbs in improving stress and fertility were not

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Data Collection Procedures

An Article Abstraction Form was used to extract the necessary information. The articles were analyzed based on the following topics: Name of Article, Author, Date and Publication; research method employed and conclusions reached regarding the research questions used in this paper: impact of stress on fertility, hormones impacted, impact of acupuncture on reducing stress, impact of acupuncture on improving fertility. For the clinical trials there were several other categories looked at, such as human subjects variables like number of subjects, age, gender, socio-ethnic information, if applicable, level of stress, level of anxiety, ability to conceive; phases of the menstrual cycle; stress hormones; reproductive hormones impacted by stress. In case of animal studies, the number, the type of animals and the research procedure used were analyzed. An Article Abstraction Form was completed for every article that was deemed as meeting the eligibility requirements for the current study.

Once the information from the articles was gathered, it was grouped based on overarching themes and sub-themes. Some of the themes that emerged were Stress and Anxiety and Female Fertility, Acupuncture and Stress and Anxiety, Acupuncture, Stress and Anxiety, and Female Fertility, Acupuncture Influence on the Success Rate of In-vitro Fertilization. A copy of the Article Abstraction form used in this study is included in Appendix A.

Data Analysis

Data collected from the Article Abstraction Forms were compiled, and pertinent factors were tallied wherever possible and appropriate to the research questions of the current study. Data were collated and represented in several tables. The data were analyzed to identify

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overarching themes relevant to the research questions. Analyses included both descriptive and qualitative analysis to identify themes and trends in the body of research reviewed.

Validity and Reliability

To increase validity and reliability of this study only studies that show impact of stress on bio-markers such as cortisol, estradiol, progesterone, and other HPA and HPG/HPO hormones were selected; those that used subjective measurements of stress and anxiety were eliminated.

Human Subjects Ethical Considerations

The current study was a research synthesis. As a result there were no human subjects used. This research proposal was reviewed and approved by the Yo San University Institutional Review Board (IRB), and a copy of the letter of approval is in the Appendix A of this document.

Chapter 4: Results

Data for this study included the literature that was reviewed for Chapter Two of this study. The contents of the articles were summarized using the Article Abstraction Form displayed in Appendix B, and discussed in the Methods chapter of this document. Several common threads emerged and are discussed in the following sections.

Stress and Anxiety and Female Fertility

There are many studies and various trials done to assess the impact of stress and anxiety on female fertility. Of the articles selected for this section, five are literature reviews: (Boivin, 2003; Cwickel, 2004, Ferin, 1999, Koopman, 2013, Nakamura, et al., 2008, and Nepomnaschy, et al., 2007). Three of the articles are prospective studies and experiments: (Baird, et al., 1999; Lynch, et al., 2012; Nepomnaschy, et al., 2004). All articles listed above show strong correlation between stress and anxiety and infertility except one, (Lynch, et al., 2012). In their prospective cohort study of women trying to conceive Lynch and associates found no association between most psycho-social measures and fecundability. They did, however, find an increase in the probability of conception in women who had a strong social support base. The researched articles refer to how various phases of the menstrual cycle and associated endocrine hormones are affected by stress. Table 1 shows a summary of the findings by impact of stress and anxiety on fertility, menstrual cycle impacted and hormones.

Table 1

Stress and Anxiety (S & A) – Impact on Female Fertility

Article Authors	S & A Impact on Fertility	Menstrual Phase Impacted	HPA Hormones Impacted	HPO Hormones Impacted
Baird, et alt., (1999)	Yes Observe changes in hormones to predict probability of conception	Follicular Ovulation		Estrogen, Progesterone, LH
Cwickel et alt. (2004)	Yes		CRH, ACTH, Cortisol, POMC	LH, LHRH
Ferin, (1999)	Yes	Follicular Luteal function	CRH, Vasopressin	LH, GnRH
Koopman (2013)	Yes	Ovulation IVF Implantation	Cortisol, Adrenalin	FSH, LH
Lynch et alt., (2012)	No Used self-reported psychosocial stress	Correlated with Bio-markers of stress	Cortisol	
Nakamura et alt.(2008)	Yes	Ovulation Luteal Phase Implantation	Cortisol, CRH, GC, NGF, ACTH	Estrogen Progesterone LH
Nepomnaschy et alt., (2004)	Yes	Follicular Ovulation Luteal Implantation	Cortisol	FSH, Estrogen, LH, Progesterone
Wagenmacher et alt., (2008)	Yes in sheep	LH Surge	Cortisol	LH, Estradiol, Progesterone

Acupuncture and Stress and Anxiety

To understand the role of acupuncture in improving female fertility by reducing stress and anxiety, we need to understand how acupuncture is effective at treating stress and anxiety and their side effects. Of the articles examined, there were five that specifically addressed this topic. Three articles were literature reviews: (Errington-Evans, 2012; Pilkington, et al., 2007; and Pilkington, 2010). One article was a randomized trial (Smith, et al., 2011) and one article was an animal trial on rats (Wang, et al., 2014). Each article presented positive correlation between acupuncture and improvement in stress and anxiety outcomes. Improved stress, as one of the variables in infertility, was a key component of the effect of acupuncture. The impact of acupuncture on the hypothalamic-pituitary-adrenal (HPA) axis was the focus of one of the articles (Wang, et al., 2014). Table 2 shows the impact of acupuncture on stress and anxiety, acupuncture points used, biological/hormonal impact and other impact.

Table 2

Acupuncture – Impact on Stress and Anxiety

Article Authors	Reduction in Stress and Anxiety	Acupuncture Points	HPA/HPO Hormones Impacted	Other Impact
Errington-Evans (2012)	Yes	GV-20, Pc-6, Ht-7, Sp-6, Yin Tang		Points selected affect directly the heart and the brain based on TCM
Pilkington et al., (2007) Pilkington (2010)	Positive findings but insufficient research evidence			
Smith et al., (2011)	Yes	5 Element CF, Upper chest Kidney points, Pc-6, Pc-5, Ht-7, Ht-5 Six sessions over 8 weeks		Less social concern; less relationship concerns; improved self-efficacy; less infertility stress; ability to cope
Wang et al., (2014)	Yes	Sp-6, Ki-9 Lr-14, Bl-23	ACTH, CRH, GC, GR	Upregulation of the protein expression of GR in the hippocampus, hypothalamic paraventricular nucleus (PVN), and downregulation of the protein expression of GR in the adrenal cortex providing balance to the HAP axis

Acupuncture, Stress and Anxiety, and Female Fertility

Five articles were reviewed that had specific focus on the impact of acupuncture on the improvement of female fertility by reducing stress and anxiety. Of the five articles, two were literature reviews (Chang, et al., 2002; Ng, et al., 2008). One was a randomized control trial (Smith, et al., 2011). One was an experimental study on rats (Chen, et al., 1997), and one was a

The Impact of Acupuncture on Improvement of Female Fertility through Reduction of Stress and Anxiety questionnaire survey (Bovey, et al., 2010). Chen, et al. (1997) found that electro-acupuncture (EA) may normalize the dysfunction of the hypothalamic-pituitary-ovarian axis (HPOA) and certain endocrine fertility hormones. EA may also have this impact based on specificity of the points used. Table 3 summarizes the data by showing the impact of acupuncture on fertility improvement by reducing stress and anxiety, acupuncture points used, biological/hormonal impact, and other impact.

Table 3

Acupuncture – Impact on Fertility by Reducing Stress and Anxiety

Article Authors	Improvement in Fertility	Acupuncture Points	Biological Impact	Other Impact
Bovey et al., (2010)	Yes		. Regulation of Menstrual Cycle . Increase in follicle stimulation /ovulation .Reduction in dysmenorrhea . Promotion of Period	. Support for better hormonal balance . Maximize IVF success
Chang et al., (2002)	Yes		. Regulation of Beta-endorphins . Balance of GnRH	. Reduce uterine artery impedance . Increase endometrial thickness
Chen et al., (1997)	Yes		GnRH, LH, E2	.Regulation of the HPO axis . Promotes function of HPA axis
Ng et al., (2008)	Yes		. Regulation of Beta endorphins	. Regulation of HPO axis . Change in uterine blood flow and motility

The Influence of Acupuncture on the Success Rate of In-Vitro Fertilization (IVF)

By far the largest body of research related to acupuncture's role in the successful fertility results by reducing stress and anxiety was found in the area of IVF, and specifically acupuncture intervention before and after embryo transfer (ET). There are more trials done in this domain than in other areas of acupuncture. For this paper there were nine articles selected. Two are research reviews (Anderson, et al., 2013; Qu, et al., 2012). Seven of the articles are controlled trials (Balk, et al., 2010; Dieterle, et al., 2006; Magarelli, et al., 2009; Moy, et al., 2011; Paulus, et al., 2002; Turner, et al., 2013; and Westergaard, et al., 2006). All the articles emphasize the positive role of acupuncture on improvement of IVF outcomes. Some calculated that 64.7% of women undergoing acupuncture treatment in conjunction with IVF achieved pregnancy as compared to 42.5% of the non-acupuncture group (Balk, et al., 2010). Others showed a clinical pregnancy rate and ongoing pregnancy rate of 33.6% with acupuncture versus a 28.4 % without acupuncture (Dieterle, et al., 2006). Table 4 summarizes the data from these articles by showing the impact of acupuncture on IVF, Acupuncture Points, Biological/Hormonal Impact, and Other Impact.

Table 4

Acupuncture - Impact on IVF Outcomes

Article Authors	Improvement in IVF Outcome	Acupuncture Points	HPA Hormones Impacted	HPO Hormones Impacted
Anderson et alt., (2013)	Difficult to assess because of methodology			
Balk et alt. (2010)	Yes 64.7% vs. 42.5% pregnancy	After ET: Ren-4, Ren-6, St-29, Pc-6, Sp-10, Sp-8; Seeds on Ear Pts. Shenmen, Zigong, Neifenmi, Pizhixia 3 Days after ET: Li-4, Sp-6, St-36, Ki3, Lr-3	-Endorphins (Sympatho-inhibitory) -Luteal Phase	
Magarelli et al., (2009)	Yes 26% increase Ac. Normalized levels of cortisol and prolactin	Cridennda/ Magarelli Protocol – includes the Paulus Protocol	Cortisol	Prolactin
Moy et al., (2011)	Yes but no significant difference between true and sham acupuncture			
Paulus et alt., (2012)	Yes 42.5% vs. 26.3%	Before ET: Pc-6, Sp-8, Lr-3, GV-20, St-29 After ET: St-36, Sp-6, Sp-10, Li-4 + Ear Points: Shenmen, Zigong, Neifenmi, Naodian		
Turner et al., (2013)	Assessed that lower level of stress and anxiety on the day prior to oocyte retrieval achieved higher pregnancy rates	No acupuncture treatments		

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Westergaard et al., (2006)	<p>Yes</p> <p>Before and after ET: 39% vs 26% and 2 days after ET: 36% vs 22%</p>	Paulus Protocol		LH, Progesterone
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Chapter 5: Discussion

This study researched the impact of Acupuncture on improvement of female fertility through reduction of stress and anxiety. It looked at how stress and anxiety can negatively impact fertility in women, how acupuncture can reduce stress and anxiety, and how acupuncture can improve female fertility through the reduction of stress and anxiety.

Stress and anxiety are challenges to the homeostasis of the body, specifically causing an imbalance of the HPA axis. Research has shown a possible correlation between the HPA and the HPG/HPO axes whereby an imbalance in the hormones of the HPA axis because of stress and anxiety could effect a dysfunction in the hormones of the HPG/HPO axes (Cwikel, et al., 2004; Nepomnaschy et al., 2004; Nakamura et al. 2008; Magarelli et al., 2009). For example, increased levels of CRH seem to impact the pulsatility of the GnRH and increased levels of cortisol seem to reduce the response of the pituitary gland to GnRH disturbing the balance of the LH and FSH. Stress has also been shown to cause imbalances in progesterone and estradiol. When the aforementioned hormones get out of balance they have a negative effect on all phases of the menstrual cycle thus preventing conception. While all the articles researched showed a clear potential correlation between the HPA and HPG/HPO axes, Lynch and associates (2012) found no association between most psychological measures, stress biomarkers, and fecundability ratio. One reason this might be is that the women in the study did not report high levels of stress and anxiety.

How can acupuncture improve fertility by reducing stress and anxiety? Acupuncture may restore homeostasis of the HPA and the HPG/HPO axes, furthering the body's own ability to restore its health, as demonstrated in several studies:

- Animal studies on rats performed by Wang and associates (2014) show that when the rats were exposed to stress there was a decrease of GRs expression in the hypothalamus and in the pituitary gland and an increase in GRs expression in the adrenal cortex, commensurate with the chronic stress response. Acupuncture achieved a dual-directional regulation of the GRs expression: it down regulated the GRs expression in the adrenal cortex and up regulated the GRs expression in the hypothalamus and the pituitary, helping to inhibit the stress response. Acupuncture was also shown to reduce the CRH expression in the hypothalamus and pituitary and to inhibit the ACTH receptors in the pituitary and adrenal cortex. The use of Lr-14 and Bl-23 was more effective than the use of Sp-6 and Ki-9, proving that point specificity matters. Acupuncture seems to have achieved homeostasis of the HPA axis therefore positively acting on the HPG/HPO axes.
- A series of experimental studies were performed on 10 chronically anovulatory women and on ovariectomized rats to assess the impact of electro-acupuncture on the regulation of the HPO axis (Chen, B. Y., 1997). Among the conclusions reached from the experiments were: electro-acupuncture has a regulatory action on the HPO axis and it may be through the impact on the HPA axis. The women who were subjected to electro-acupuncture and achieved ovulation showed a

reduction in or a normal level of beta-endorphins while the beta-endorphins of the anovulatory women were of a substantially higher level. In addition, ovulatory women due to EA showed normalized levels of LH and FSH. From the experiments on the rats, Chen concluded that electro-acupuncture normalized the level of estrogen in the ovariectomized rats with lower than normal estrogen level. They noticed an increase of the adrenal glands after EA and hypothesized that the changes in the level of estrogen could potentially be due to the action of EA on the HPA axis: the acupuncture may increase the synthesis and release of adrenal corticosteroids, including androgen. Androgen can be transformed into estrogen, restoring the negative feedback on the HPO axis. In addition, GnRH and LH could be normalized through the ability of EA to accelerate the release of brain and pituitary beta-endorphins.

- Acupuncture has been shown to have potential benefits on improving the results of IVF procedures by restoring balance to cortisol and prolactin in women who were stressed when undergoing ET (Magarelli, et al., 2009).
- Acupuncture could play a role in increasing the rate of pregnancy of IVF by regulating the levels of beta-endorphins and the HPO axis (Chang, et al., 2002; Ng, et al., 2008).

Based on the analysis of the research articles selected it appears that acupuncture could play a major role in the improvement of fertility by reducing stress and anxiety and it could complement Western approaches to infertility, including IVF.

Implications for Theory

One of the gaps this study aimed to address was the reduced integration of acupuncture with western fertility medicine approaches. By using research articles that looked at the bio-markers of stress and fertility to assess the role of acupuncture in improving fertility this paper has established a language vehicle conducive to integration of acupuncture theory and action into Western medicine from a Western perspective. This will allow a better understanding of the role acupuncture can play in an integrated environment. Acupuncture theory and specifically Traditional Chinese Medicine (TCM) has its own language and theory and much remains to be done to establish commonalities between Eastern and Western approaches to diagnosis and treatment. For example, in TCM, stress could be interpreted as liver qi stagnation or heart heat or several other differential diagnoses which remain unknown to a Western doctor without extensive training in TCM. To train Western doctors in TCM may be impractical; therefore the role of acupuncturists may have to be expanded to include training and educating as well as getting a better understanding of Western diagnosis. And maybe an understanding needs to get developed regarding the fact that there are differences that can only be overcome in an actual integrated practice. More emphasis should be placed on elevating the acupuncture profession at an equal level to Western medicine so that there will be a cooperation of equals. This will provide benefits to the patients and to the medicine field as a whole.

Implications for Practice

This research synthesis highlighted the role stress and anxiety play in infertility and the ability of acupuncture to improve fertility through the reduction of stress and anxiety. This

information is only valuable if it is implemented in practical ways. Following are some recommendations for practice:

- Consider stress and anxiety as potentially being the main cause of infertility in idiopathic infertility cases and consider using acupuncture to bring the body to homeostasis and improve fertility.
- Bring awareness about the topic of this paper to medical doctors, reproductive endocrinologists, and acupuncturists in an effort to integrate their practices.
- Teach the general public about the impact stress and anxiety have on fertility in an effort to raise awareness about the importance of controlling stress and anxiety.
- Develop training materials to help with management of stress and anxiety such as yoga, tai-qi, qi-gong, meditation, and other modalities.

It is also anticipated that this study could bridge the gap we have today in our understanding related to the role that stress and anxiety play in infertility and it could offer valuable information to several segments of the larger community:

- Existing and future mothers. They could gain information about the effects of stress and anxiety on conception and the value of acupuncture in achieving their goals of successful pregnancy. It is hoped they could also pay attention to avoiding or coping with stressful situations in their lives.
- Acupuncturists. Knowledge obtained through this study could improve their practice and potentially expand their patient base.
- Urban developers. Awareness about the role of stress and anxiety on reproduction may provide another variable to consider when new social programs or buildings are

implemented.

- Students. This study could serve as a reference to those students interested in the topics covered by this study.
- Western Medicine. The study could show practitioners of the Western Medicine the potential role stress and anxiety can play in infertility and how acupuncture could be potentially integrated into the treatment of infertility due to stress and anxiety.
- Researchers. The study could serve as reference material to other researchers.

Limitations of the Current Study

Given that this project is a research synthesis, the first limitation is the reliance on other researchers' data obtained through the internet and no first-hand experience from trials or randomized controlled studies. In addition, there were only a few articles of research selected from a myriad of articles that exist so the information obtained to substantiate the research questions is relatively limited. Another limitation is in the fact that the studies related to the interested topic were not cohesive; there were no studies that researched the broad spectrum of the entire menstrual cycle as it relates to the impact of stress and anxiety and to acupuncture and fertility. The conclusions of this study had to be made based on integration of various discreet pieces of research. Another limitation relates to the fact that a large body of research performed in China in the domain of acupuncture was unavailable because of language barriers. The qualitative analysis of the data may pose a limitation because it is more subjective and does not benefit from the objectivity of statistical analysis. One more limitation could be the fact that this study focused only on the bio-markers of stress and fertility and omitted most research that analyzed subjective stress factors which could also have an impact

The Impact of Acupuncture on Improvement of Female Fertility through Reduction of Stress and Anxiety on fertility.

Recommendation for Future Research

More research is needed to further understand and prove the role of acupuncture in improvement of female fertility by reducing stress and anxiety. Future studies should include larger sizes of participants based on experience from past research and account for the impact of confounders. In addition, the acupuncture treatments should be more detailed and fixed based on the patient's TCM diagnosis and there should be more explanation provided as to why a certain treatment should be used. Needling should be more standardized and follow certain protocols (Qu, Fan, Zhou, Jue, Bovey, Mark, Franconi, Giovanna, Chan, Kelvin, University of Western Sydney, Smith, Caroline, Robinson, Nicola, 2012).

Better defined and broader spectrum research objectives should be established to look at the entire menstrual cycle and measure the impact of stress and anxiety on each phase of the cycle and to correlate each phase to the HPA axis activity and the impact of acupuncture. The experience of the acupuncturists performing the needling should also be governed by predetermined standards to ensure consistency of treatment. There remain some other areas of conflict that should get more consideration as future studies are performed: clear TCM diagnosis and individualized treatments versus fixed protocols required by the scientific method; acupuncture dosage (number of points needled and number of treatments), frequency of treatments; duration of treatment (which could also be dependent of the individual patient's needs), and prior acupuncture experience of the patient (Anderson, B., & Rosenthal, L., 2013).

Conclusion

Stress and anxiety appear to play a significant role in infertility through their impact on the HPA axis and HPG/HPO axes respectively. Hormonal imbalances in the HPA axis seem to effect hormonal changes in the HPG/HPO axis disturbing the fine balance needed for follicle development, LH surge, ovulation, endometrium development, and implantation. Acupuncture may have a regulatory effect on the HPA and HPG/HPO axes by enabling physiological balance of the body. By restoring homeostasis, acupuncture could possibly help the body get back its own capacity to restore health and allow for healthy reproduction of life.

References

- Anderson, B., & Rosenthal, L. (2013). Acupuncture and in vitro fertilization: Critique of the evidence and application to clinical practice. *Complementary therapies in clinical practice, 19*(1), 1-5.
- Baird DD, Weinberg CR, Zhou H, Kamel F, McConnaughey DR, Kesner JS, Wilcox AJ. (1999). Preimplantation urinary hormone profiles and the probability of conception in healthy women. *FertilSteril 71:40–49*.
- Balk, J., Catov, J., Horn, B., Gecki, K., & Wakim, A. (August 01, 2010). The relationship between perceived stress, acupuncture, and pregnancy rates among IVF patients: A pilot study. *Complementary Therapies in Clinical Practice, 16, 3, 154-157*.
- Boivin, J. (2003). A review of psychosocial interventions in infertility. *Social science & medicine, 57*(12), 2325-2341.
- Bovey, M., Lorenc, A., & Robinson, N. (December 01, 2010). Extent of acupuncture practice for infertility in the United Kingdom: experiences and perceptions of the practitioners. *Fertility and Sterility, 94, 7, 2569-2573*.
- Chang, R., Chung, P. H., & Rosenwaks, Z. (2002). Role of acupuncture in the treatment of female infertility. *Fertility and sterility, 78*(6), 1149-1153.
- Chen, B. Y. (1997). Acupuncture normalizes dysfunction of hypothalamic-pituitary-ovarian axis. *Acupuncture and Electro Therapeutics Research-the International Journal, 22*(2), 97-108.
- Chrousos, G. P., Loriaux, D. L., & Gold, P. W. (1988). Introduction: The concept of stress and its historical development. In *Mechanisms of physical and emotional stress* (pp. 3-7). Springer US.

The Impact of Acupuncture on Improvement of Female Fertility through Reduction of Stress and Anxiety

Cooper, H. M., & Cooper, H. M. (2010). *Research synthesis and meta-analysis: A step-by-step approach*. Los Angeles: Sage.

Cwikel, J., Gidron, Y., & Sheiner, E. (2004). Psychological interactions with infertility among women. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, *117*(2), 126-131.

Dieterle, S., Ying, G., Hatzmann, W., & Neuer, A. (2006). Effect of acupuncture on the outcome of in vitro fertilization and intracytoplasmic sperm injection: a randomized, prospective, controlled clinical study. *Fertility and sterility*, *85*(5), 1347-1351.

Errington-Evans, N. (2012). Acupuncture for anxiety. *CNS neuroscience & therapeutics*, *18*(4), 277-284.

Farlex Partner Medical Dictionary © Farlex 2012

Ferin M. (1999). Stress and the reproductive cycle. *J ClinEndocrMetab* *84*:1768–1774.

Hamilton, B. E., & Sutton, P. D. (2012). Recent trends in births and fertility rates through June 2012. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, Division of Vital Statistics.

Koopman, J. (2013). The Experimental Effects of Stress on Fertility. *Berkeley Scientific Journal*, *18*(1).

Levine, S. (2005). Developmental determinants of sensitivity and resistance to stress. *Psychoneuroendocrinology*, *30*(10), 939-946.

Lynch, C. D., Sundaram, R., Buck Louis, G. M., Lum, K. J., & Pyper, C. (2012). Are increased levels of self-reported psychosocial stress, anxiety, and depression associated with fecundity? *Fertility and sterility*, *98*(2), 453-458.

The Impact of Acupuncture on Improvement of Female Fertility through Reduction of Stress and Anxiety

Ma, Y., Ma, M., & Cho, Z.-H. (2005). *Biomedical acupuncture for pain management: An integrative approach*. St. Louis, Mo: Elsevier Churchill Livingstone.

Magarelli, P. C., Cridennda, D. K., & Cohen, M. (2009). Changes in serum cortisol and prolactin associated with acupuncture during controlled ovarian hyperstimulation in women undergoing in vitro fertilization–embryo transfer treatment. *Fertility and sterility*, *92*(6), 1870-1879.

Moy, I., Milad, M. P., Barnes, R., Confino, E., Kazer, R. R., & Zhang, X. (2011). Randomized controlled trial: effects of acupuncture on pregnancy rates in women undergoing in vitro fertilization. *Fertility and Sterility*, *95*(2), 583-587.

Nakamura, K., Sheps, S., & Arck, P. C. (January 01, 2008). Stress and reproductive failure: past notions, present insights and future directions. *Journal of Assisted Reproduction and Genetics*, *25*.

Nepomnaschy, P. A., Welch, K., McConnell, D., Strassmann, B. I., & England, B. G. (2004). Stress and female reproductive function: a study of daily variations in cortisol, gonadotrophins, and gonadal steroids in a rural Mayan population. *American Journal of Human Biology*, *16*(5), 523-532.

Nepomnaschy, P. A., Sheiner, E., Mastorakos, G., & Arck, P. C. (2007). Stress, immune function, and women's reproduction. *Annals of the New York Academy of Sciences*, *1113*(1), 350-364.

Ng, E. H., So, W. S., Gao, J., Wong, Y. Y., & Ho, P. C. (January 01, 2008). The role of acupuncture in the management of subfertility. *Fertility and Sterility*, *90*, 1, 1-13.

Paulus, W. E., Zhang, M., Strehler, E., El-Danasouri, I., & Sterzik, K. (April 01, 2002). Influence of acupuncture on the pregnancy rate in patients who undergo assisted reproduction therapy. *Fertility and Sterility*, *77*, 4, 721-724.

The Impact of Acupuncture on Improvement of Female Fertility through Reduction of Stress and Anxiety

Pease, R. W., & Merriam-Webster, Inc. (2006). *Merriam-Webster's medical dictionary*.

Springfield, Mass: Merriam-Webster Inc.

Pilkington, K. (2010). Anxiety, depression and acupuncture: a review of the clinical research.

Autonomic Neuroscience, 157(1), 91-95.

Pilkington, K., Kirkwood, G., Rampes, H., Cummings, M., & Richardson, J. (2007). Acupuncture for anxiety and anxiety disorders—a systematic literature review. *Acupuncture in Medicine*, 25(1-2), 1-10.

Qu, Fan, Zhou, Jue, Bovey, Mark, Franconi, Giovanna, Chan, Kelvin, University of Western Sydney, Smith, Caroline, Robinson, Nicola. (2012). *Does acupuncture improve the outcome of in vitro fertilisation? Guidance for future trials*. Germany, Urban und Fischer Verlag.

Rosch, P. J. (1998). Reminiscences of Hans Selye and the birth of 'stress'. *Stress Medicine*, 14(1), 1-6.

Smith, C. A., Ussher, J. M., Perz, J., Carmady, B., & de, L. S. (January 01, 2011). The effect of acupuncture on psychosocial outcomes for women experiencing infertility: a pilot randomized controlled trial. *Journal of Alternative and Complementary Medicine (New York, N.Y.)*, 17, 10, 923-30.

Turner, K., Reynolds-May, M. F., Zitek, E. M., Tisdale, R. L., Carlisle, A. B., & Westphal, L. M. (January 01, 2013). Stress and anxiety scores in first and repeat IVF cycles: a pilot study. *Plos One*, 8, 5.)

United States & National Institutes of Health (U.S.). (2003). *Medline Plus: Medical dictionary*.

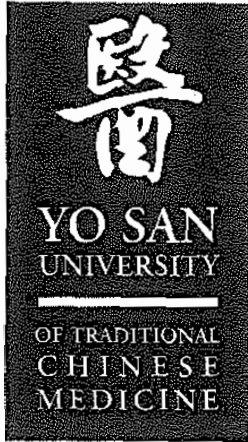
Bethesda, MD: National Institutes of Health. Department of Health and Human Services.

The Impact of Acupuncture on Improvement of Female Fertility through Reduction of Stress and Anxiety

Wagenmaker, Elizabeth; Breen, Kellie; Oakley, Amy; Pierce, Bree; Tilbrook, Alan; Turner, Anne; & Karsch, Fred. (2008). *Cortisol interferes with the estradiol-induced surge of luteinizing hormone in the ewe*. Society for the Study of Reproduction.

Wang, S. J., Zhang, J. J., & Qie, L. L. (2014). Acupuncture Relieves the Excessive Excitation of Hypothalamic-Pituitary-Adrenal Cortex Axis Function and Correlates with the Regulatory Mechanism of GR, CRH, and ACTHR. *Evidence-Based Complementary and Alternative Medicine, 2014*.

Westergaard, L. G., Mao, Q., Kroglund, M., Sandrini, S., Lenz, S., & Grinsted, J. (2006). Acupuncture on the day of embryo transfer significantly improves the reproductive outcome in infertile women: a prospective, randomized trial. *Fertility and Sterility, 85*(5), 1341-1346.



APPENDIX A – IRB Approval Letter

March 28th, 2014

Gigi B. Cristache, Dipl.Ac., R.Ac.
30426 Knighton Dr.
Farmington Hills, MI 48331

Dear Gigi,
Your revised research proposal has been approved, with no additional recommendations effective through March 31, 2015.

Should there be any significant changes that need to be made which would alter the research procedures that you have explained in your proposal, please consult with the IRB coordinator prior to making those changes.

Sincerely,

Penny Weinraub, LAc.

Penny Weinraub, LAc.
IRB Coordinator

APPENDIX B – Article Abstraction Form

Name of Article	Author	Publication
Date		
Research Method		
Research Question/Statement		
Conclusions Reached		
Impact of stress on fertility		
Hormones impacted		
Impact of acupuncture on reducing stress		
Impact of acupuncture on improving fertility		
Human Subjects		
Number of subjects		
Age		
Gender		
Socio-ethnic information		
Weight		
Height		
Prior pregnancies		
Level of stress		
Level of anxiety		
Ability to conceive		
Phases of the menstrual cycle		
Stress hormones analyzed		
Reproductive hormones impacted by stress		
Animal Subjects		
Type		
Number of animals		
Information on prior illness		
Information on subjects' diet		
Involvement of acupuncture		
Points used		
Number of treatments		
Frequency of treatments		
Duration of treatment		
Involvement of Chinese herbs		
Herbs studied		
Dosage		
Frequency of use		
Duration of use		
Other treatment modalities used		
Hormone level after acupuncture		